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Correlation between otic capsule density and serum 25(OH)D with hearing threshold in chronic kidney disease



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ABSTRACT

Background: Prevalence of hearing loss in chronic kidney disease is between 40–60%. Its pathomechanism has not been fully understood but could be related to temporal bone remodeling. The bone metabolism disorder in chronic kidney disease is also manifested in vitamin D deficiency.

Purpose: This study aims to learn the correlation between otic capsule density and serum 25(OH)D with a hearing threshold in chronic kidney disease without hemodialysis.

Method: An observational analytic study with a cross-sectional design involving 36 patients with stage 3 and 4 chronic kidney disease. Hearing was examined with Interacoustics AA222 audiometer, otic capsule density was measured using Toshiba Aquilion 128 CT while vitamin D was assessed by ELISA using ORGENTEC 25-OH Vitamin D3/D2 Assay kit. Hearing loss was defined as a hearing threshold over 25 dB on the better hearing ear.

Results: Hearing loss was found in 17 of 36 subjects (47.2%). On independent sample t-test, ears with HL (n=44) has lower otic capsule density than ears without (n=28) significantly ($p < 0.05$; ROI1: 1.867 ± 285 vs 2.095 ± 315 HU; ROI2: 1.864 ± 190 vs 2.051 ± 293 HU). Pearson test showed a significant negative correlation between otic capsule density and hearing threshold ($p < 0.05$; ROI1: $r = -0.427$; ROI2: $r = -0.402$). Serum 25(OH)D was insignificantly lower in a subject with HL (n=17) than without ($p > 0.05$; 16.45 ± 6.33 vs. $17.99 + 10.57$ ng/mL) and no correlation was found to a hearing threshold in chronic kidney disease.

Conclusion: Significant correlation was found between otic capsule density and hearing threshold in predialysis chronic kidney disease. There were no correlation between serum 25(OH)D and hearing threshold and therefore unsuitable as a biomarker for the aforementioned condition.

Keywords: chronic kidney disease, hearing loss, vitamin D, bone metabolism, temporal bone

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INTRODUCTION

Hearing loss in Chronic Kidney Disease (CKD) is common with a prevalence of 40–60% in numerous research. Cochlear was thought to be the main site of lesion since the condition is sensorineural and there are similarities between it and kidney's glomerulus in term of embryology, anatomical structure, function, and influence of drugs. This relationship is also termed oto–renal axis.¹⁻³

Nevertheless, the exact pathomechanism for this condition is not fully understood. Studies in Australia and South Korea showed that glomerular filtration rate less than 60 mL/min/1.73 m² to be a risk factor for hearing loss. Independent of hypertension and diabetes, which are shared comorbidities by hearing loss and CKD.^{4,5} Types and duration of treatment, such as hemodialysis or ototoxic/nephrotoxic medication has been found to be inconsistent to hearing loss prevalence.⁶ There were lack of correlations observed in blood test parameters, the most frequent workup done for management of CKD.^{7,8}

Recently, the association was observed between CT evaluation of temporal bone and hearing loss

in CKD. The inner ear is located in a petrous part of temporal bone known as otic capsule. Erkok reported that otic capsule density was significantly lower in ears with hearing loss than ears without hearing loss. There was also a negative correlation between the densitometric value to hyperparathyroid hormone level and duration of hemodialysis.⁹ These findings suggest further evaluation on bone metabolism role in hearing loss in CKD.

Metabolic bone disorder is a common complication of CKD. Phosphate retention decreased synthesis of calcitriol and alteration in parathyroid gland could eventually result in vascular calcification and mortality.¹⁰ One of the management for this condition is evaluation and supplementation of 25(OH)D, which act as pre-hormone for vitamin D.

Substrate limitation, either by lower production (decreased sunlight intake) or increased loss (proteinuria) could further impair the diseased renal 1- α hydroxylase activation of 25(OH)D into 1,25(OH)₂D₃.¹¹

However there is evidence of extrarenal activation in producing calcitriol, Thus maintaining

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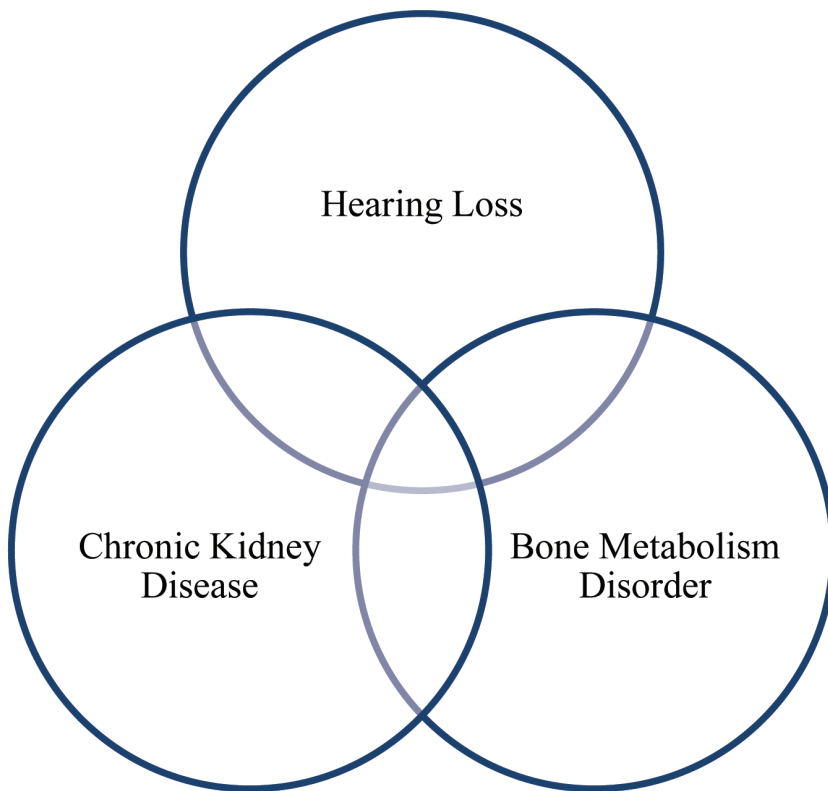


Figure 1 Relationship between hearing loss, chronic kidney disease, and bone metabolism disorder

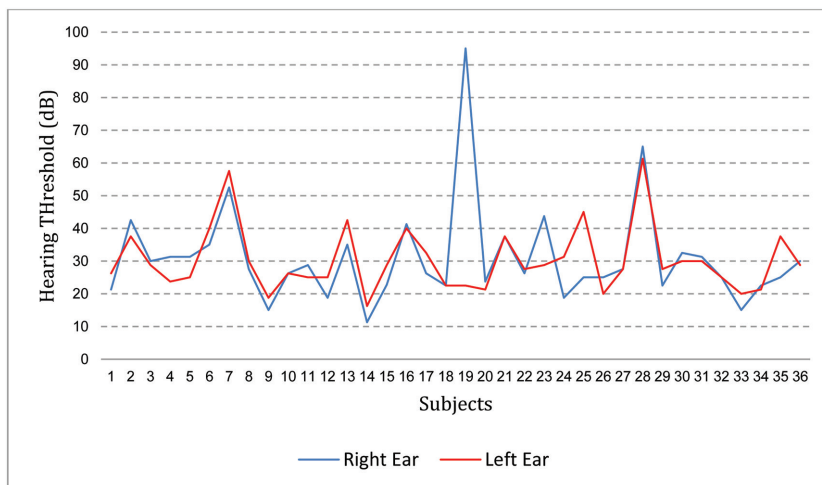


Figure 2 Hearing thresholds for 36 subject's right and left ear (n=72)

serum 25(OH)D levels above 20 ng/mL is still recommended on renal failure with evidence of reducing mortality.¹²

Meanwhile, Osteopathy resulting in hearing loss can be observed in many conditions such as otosclerosis and Paget disease.¹³⁻¹⁵ Upala et al. reported that even age-related hearing loss or presbycusis is associated with osteoporosis in their meta-analysis.¹⁶ The pathology lies at the temporal bone, which is the hardest bone in human. While demineralization occurs exclusively at the otic

capsule in otosclerosis, it is interesting to learn whether systemic bone metabolic disorder (Paget, osteoporosis, and CKD) could alter temporal bone metabolism, which is very low in normal condition to the extent that post-traumatic temporal bone fractures do not heal. However, since radiologic evaluation in CKD is uncommon, it would be beneficial in practice to link blood parameters featured in both hearing loss and CKD, such as 25(OH)D.

There are past reports of low vitamin D levels on patients with sensorineural hearing loss.^{17,18} Ikeda compared hearing loss in renal failure to vitamin D insufficiency and suggests perilymph hypocalcemia and reduced cochlear potential as the underlying process.¹⁹ Zou et al. reported a progressive hearing loss in mice with deleted vitamin D receptor, supporting the previous finding on the subject.²⁰

METHODS

This is an observational study with a cross-sectional design. Data was collected after ethical clearance had been obtained. Patients who visited Internal Medicine Outpatient Clinic in Saiful Anwar Public Hospital, Malang were screened and evaluated for Glomerular Filtration Rate. Inclusion criteria were: stage 3 or 4 CKD, treatment for more than 3 consecutive months and within 19–65 years of age. Subjects with congenital deafness, ear deformity, and otoscopic abnormalities on external/middle ear were excluded. After consenting, the subject went through audiometry, peripheral blood sampling for vitamin D and temporal bone CT within the same day.

The hearing was examined with an Interacoustics AA222 audiometer; otic capsule density was measured using Toshiba Aquilion 128 CT while vitamin D was assessed by ELISA using ORGENTEC 25-OH Vitamin D3/D2 Assay kit.

Hearing threshold was defined as the mean of lowest pure-tone intensity which can be identified by the subject in 500, 1000, 2000, and 4000 Hz. Hearing loss was defined as a hearing threshold over 25 dB. Subjects were assessed for hearing loss based on their better hearing ear.

Variables were checked for normality using Kolmogorov–Smirnov test. Correlation to normally distributed variables was assessed with Pearson Correlation Test.

RESULTS

Thirty-six patients enrolled for this study during June–October 2016, consisting of 18 males and 18 females. Mean of age were 51.36 +/- 8.89 years.

Table 1 Comparison of otic capsule density between hearing loss ears and normal ears

	HL ears(n=44)	Normal ears (n=28)	p
ROI1 (HU)	1.867 ± 285	2.095 ± 315	0.002*
ROI2 (HU)	1.864 ± 190	2.051 ± 293	0.002*

Table 2 Correlation between otic capsule density and hearing thresholds

	ROI 1		ROI 2	
	r	p	r	p
Hearing Thresholds	-0.427	0.000*	-0.402	0.000*
500 Hz	-0.274	0.020*	-0.281	0.017*
1000 Hz	-0.403	0.000*	-0.387	0.001*
2000 Hz	-0.401	0.000*	-0.340	0.003*
4000 Hz	-0.401	0.000*	-0.390	0.001*

Table 3 Correlation between serum 25(OH)D and hearing threshold and otic capsule density variables

	25(OH)D	
	r	p
Hearing Threshold	-0.007	0.968
ROI 1	0.061	0.723
ROI 2	0.101	0.560

Hypertension, diabetes, ototoxic drug, and loud noise exposure were found by 77.78, 63.89, 13.89, and 22.22 percent of subjects respectively. All subject underwent hearing assessment by pure-tone audiometry on both ears. There was no air-bone gap nor conductive hearing loss assessed. Assessing each ear separately, it was found 44 out of 72 ears had hearing loss. From tympanometry, Jerger type A and as was examined in 41 and 27, respectively. By individuals, there were 17 of 36 subjects with hearing loss on their better hearing ear. No significant difference was observed based on risk factor and renal function test value between individuals with and without hearing loss.

On CT-Scan, otic capsule density was measured on 1 mm anterior to oval window (Region of Interest 1/ROI1) and on 1 mm anterior to the internal auditory canal (Region of Interest 2/ROI2). From 72 ears, the mean value for ROI1 and ROI 2 were 1.956 /- 315 and 1.937 + 251 Hounsfield Unit (HU) respectively.

No subject had serum 25(OH)D level above 30 ng/mL and 69.5% subjects had below 20 ng/mL. The mean value for 36 subjects was 17.26 +/- 8.74 ng/mL.

Ears with hearing loss have significantly lower otic capsule density ($p < 0.05$) on both ROI1 and ROI2 variables, as shown by independent sample t-test.

Based on Pearson correlation test, otic capsule density showed significant negative correlation with numerical values of hearing threshold ($p < 0.05$). Further analysis showed similar results to 500, 1000, 2000, and 4000 Hz frequency.

However, serum 25(OH)D showed no correlation either to hearing threshold nor otic capsule density based on subjects with the better hearing ear.

DISCUSSION

Bone remodeling of the otic capsule has been found to be associated with hearing loss in renal failure. Erkoç's study population was patients undergoing hemodialysis for stage V CKD. While our study was conducted at an earlier stage of CKD, the results were similar in that ears with hearing loss had significantly lower density than normal ears. Furthermore, our study found a significant negative correlation between otic capsule density and numerical values of the hearing threshold for all 72 ears.

Poorer hearing threshold with a lower density of otic capsule suggests the role of temporal bone in the mechanism of hearing. Monsell suggested that acoustic energy is being absorbed by lower density (Paget) bones and results in lower amplitude displacement of the basilar membrane, in reference to von Bekesy's "Travelling Wave" theory.¹³ It was widely believed that movement of endolymph is responsible for action potential of hair cells, but the importance of otic capsule as a structural integrity supports the earlier Helmholtz 'Resonance' theory. To resonate with lower intensity stimulus, outer hair cell utilizes pressure kept within a solid container.²¹ No other bone in human body is as hard as the temporal bone.

Other than the anatomical factor, the hearing could also be affected by bone remodeling process as an inflammatory factor. Cytokines released from bony labyrinth during the osteoclastic process was thought to diffuse within the membranous labyrinth, resulting in injury to the cochlea.²³

The key regulator of low bone metabolism in temporal bone is osteoprotegerin. This protein inhibits osteoclastogenesis activity. Studies showed that otic capsule had the highest concentration of osteoprotegerin, suggesting that membranous labyrinth produces it locally.^{23,24} This theory is supported by our finding of otic capsule density in one individual with the left profound sensorineural hearing loss. The patient had suffered from sudden deafness, a form of cochlear dysfunction. The normal ear densitometric value was 1877 HU while the affected ear was 1193 HU. It should be noted that

osteoprotegerin metabolism is also altered in CKD and is currently under research as a biomarker for vascular calcification.²⁵ Further researches would be needed to learn whether osteoprotegerin influenced renal induced hearing loss

The more obvious factor of bone metabolism is, of course, the parathyroid hormone. Since it was not feasible to be checked in our facilities, we tried to associate bone remodeling in CKD to serum 25(OH)D. Serum 25(OH)D is recommended to be routinely evaluated, affordable and has also been linked to hearing loss in both human and animal studies. Although serum 25(OH)D levels in subjects with hearing loss are slightly lower than the normal subject, there was no statistical significance. There was no correlation between serum 25(OH)D and hearing threshold nor otic capsule density. The lack of direct relationship between serum 25(OH)D and bone density was also observed by Kota et al. even when 25(OH)D was negatively associated with parathyroid hormone, and parathyroid hormone was negatively associated with bone density.^{26,27} Moderate negative correlation between hearing thresholds and otic capsule density highlights the structural role of temporal bone in hearing physiology. It seems that in contrast to past studies, serum 25(OH)D is unrelated to hearing loss.

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